Remarks

Amendments to the Claims

Independent claims 1 and 48 are amended to incorporate:

- subject matter recited in canceled dependent claims 2, 4, 5, 6, 8, 9, 11, and 50; and
- subject matter canceled from dependent claims 7, 10, 64, and 65.

Amendments consistent with the changes to claims 1, 46, and 48 are made to dependent claims 3, 7, 10, 12-15, 23-29, 37-41, 47, 60, 64, and 65 and to withdrawn claims 16-19, 30-36, 51-59, 71, 76, 79, and 80.

Dependent claim 3 and independent claims 46 and 48 are amended to recite an "artificial" particle. Artificial particles are taught in paragraphs [40]-[45]. New claims 143, 144, and 145 depend from claims 3, 46, and 48, respectively, and recite that the artificial particle is a bead. The specification discloses artificial particles which are beads in [29] and [160].

The amendments add no new matter.

Inventors' Declaration

The Office Action contends the inventors' declaration is defective because changes made to Dr. Oelke's address were initialed but not dated. A new declaration has been requested and will be filed as soon as it is available.

Objection to the Specification

The Office Action objects to the specification because the trademark "GOLGISTOP" was not properly indicated. As requested, the specification has been amended to indicate this trademark and to include generic terminology.

Please withdraw the objection.

Rejections Under 35 U.S.C. § 102(e)

The Office Action contains three rejections under 35 U.S.C. § 102(e):

- independent claims 1 and 48 and dependent claims 2-6, 12-15, 23-29, 37-41, 49, and 50 over Albani, US 2002/0122818 (item 8 of the Office Action);
- independent claims 1 and 48 and dependent claims 2-9, 12-15, 27, 28, 37, 39-41, 49, 50, 60-62, and 64 over Schneck *et al.*, U.S. Patent 6,268,411 (item 9 of the Office Action); and
- independent claims 1 and 48 and dependent claims 2-4, 8-15, 39, 40, 49, 50, 60-62, and 65 over Schneck *et al.*, U.S. Patent 6,015,884 (item 10 of the Office Action).

Claims 2, 4, 5, 6, 8, 9, 11, and 50 have been canceled. Applicants respectfully traverse the rejections of the remaining claims.

A reference cited under 35 U.S.C. § 102 must expressly or inherently describe each element set forth in the rejected claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). None of the cited references meets this standard.

Albani, US 2002/0122818

Independent claims 1 and 48 and dependent claims 3, 12-15, 23-29, 37-41, 49, 64, and 65 recite two particular molecular complexes:

- an MHC class I molecular complex comprising at least two fusion proteins, wherein a first fusion protein comprises a first MHC class I α chain and a first immunoglobulin heavy chain comprising a variable region and wherein a second fusion protein comprises a second MHC class I α chain and a second immunoglobulin heavy chain, wherein the first and second immunoglobulin heavy chains associate to form the MHC class I molecular complex, wherein the MHC class I molecular complex comprises a first MHC class I peptide binding cleft and a second MHC class I peptide binding cleft; and
- an MHC class II molecular complex comprising at least four fusion proteins, wherein (a) two first fusion proteins comprise (i) an immunoglobulin heavy chain comprising a variable region and (ii) an extracellular domain of an MHC class IIβ chain; and (b) two second fusion proteins comprise (i) an immunoglobulin light chain and (ii) an extracellular domain of an MHC class IIα chain, wherein the two first and the two second fusion proteins associate to form the MHC class II molecular complex, wherein the extracellular domain of the MHC class IIβ chain of each first fusion protein and the extracellular domain of the MHC class IIα chain of each second fusion protein form an MHC class II peptide binding cleft.

US 2002/0122818 does not disclose either type of molecular complex.

Schneck *et al.*, U.S. Patent 6,268,411

Independent claims 1 and 48 and dependent claims 3, 7, 12-15, 27, 28, 37, 39-41, 49, 60-62, and 64 recite a rigid solid support comprising one or both of the two types of particular molecular complexes discussed above and "at least one lymphocyte affecting molecule selected from the group consisting of a T cell costimulatory molecule, an adhesion molecule, a T cell growth factor, a regulatory T cell inducer molecule, and an apoptosis-inducing molecule." U.S. Patent 6,268,411 does not disclose a rigid solid support comprising either of the recited molecular complexes and any of the recited groups of lymphocyte affecting molecules.

Schneck *et al.*, U.S. Patent 6,015,884

Independent claims 1 and 48 and dependent claims 3, 10, 12-15, 39, 40, 48, 49, 60-62, 64, and 65 recites a rigid solid support comprising one of the two types of particular molecular complexes discussed above and "at least one lymphocyte affecting molecule selected from the group consisting of a T cell costimulatory molecule, an adhesion molecule, a T cell growth factor, a regulatory T cell inducer molecule, and an apoptosis-inducing molecule." U.S. Patent 6,015,884 does not disclose a rigid solid support comprising either of the recited molecular complexes and any of the recited groups of lymphocyte affecting molecules.

Neither US 2002/0122818, U.S. Patent 6,268,411, or U.S. Patent 6,015,884 teaches each and every element of the claims against which it is cited. Therefore, none of these references anticipates any of the pending claims.

Please withdraw the rejections.

Rejections Under 35 U.S.C. § 103(a)

The Office Action makes three rejections of claims 1-15, 23-29, 37, 39-41, 46-50, 60-62, 64, and 65 under 35 U.S.C. § 103(a) over the following combinations of references:

- Schneck *et al.*, U.S. Patent 6,268,411 (the '411 patent) in view of Rhode *et al.*, WO 97/28191 and Latouche[1] (item 12 of the Office Action);
- Schneck *et al.*, U.S. Patent 6,015,884 (the '885 patent) in view of WO 97/28191, Schneck *et al.*, WO 97/35991, and Latouche (item 13 of the Office Action); and
- WO 97/35991 in view of WO 97/28191 and Latouche (item 14 of the Office Action).

Claims 2, 4, 5, 6, 8, 9, 11, and 50 have been canceled. Applicants respectfully traverse the rejections of the remaining claims.

Section 103(a) of 35 U.S.C. states:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Obviousness under 35 U.S.C. § 103(a) is a question of law based on several factual inquiries:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.

[1] Latouche & Sadelain, "Induction of human cytotoxic T lymphocytes by artificial antigen-presenting cells," *Nature Biotechnology 18*, 405-09, April 2000.

Graham v. John Deere Co., 383 U.S. 1, 17 (1966). The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness based on the results of the factual inquiries under *Graham*. A *prima facie* case of obviousness has three elements:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8th ed., § 2142. In the present application, the results of the factual inquiries under *Graham v. John Deere Co.* do not support a *prima facie* case that any of claims 1, 3, 7, 10, 12-15, 23-29, 37, 39-41, 46-49, 60-62, 64, or 65 are obvious under 35 U.S.C. § 103(a).

1. Scope and content of the prior art

The first factual inquiry under *Graham* is to determine the scope and content of the prior art. 383 U.S. at 17. The scope and content of the cited prior art is described below.

a. U.S. Patent 6,268,411 (the '411 patent) in view of WO 97/28191 and Latouche

The '411 patent discloses the MHC class I molecular complex recited in independent claims 1 and 48. The '411 patent teaches that the molecular complex can be "affixed to a solid substrate, such as a glass or plastic slide or tissue culture plate or latex, polyvinylchloride, or polystyrene beads." Col. 9, lines 63-67. The '411 patent also teaches that the molecular complex can be "conjugated to molecules which stimulate an immune response, such as lymphokines or other effector molecules." Col. 10, lines 16-18. The '411 patent does not teach

or suggest a rigid, solid support comprising any costimulatory or T cell affecting molecule in combination with the MHC class I molecular complex.

WO 97/28191 teaches molecular complexes which the Office Action acknowledges differ from those recited in the pending claims.[2] The molecular complexes can be anchored to cell membranes of naturally occurring "host compatible antigen presenting cells." Page 33, lines 13-16. WO 97/28191 does not teach or suggest a rigid solid support comprising any type of molecular complex or costimulatory molecule.

Latouche teaches artificial antigen presenting cells which are fibroblasts transfected with single HLA-peptide complexes. See page 406, col. 2, last full ¶. Latouche does not teach or suggest a rigid solid support comprising any type of molecular complex or costimulatory molecule.

b. U.S. Patent 6,015,884 (the '885 patent) in view of WO 97/28191, WO 97/35991, and Latouche

The '884 patent discloses the MHC class II molecular complex recited in independent claims 1 and 48. The '884 patent teaches that the molecular complex can be "immobilized on a substrate to stimulate antigen-specific T cell responses." Col. 6, lines 10-14. The '884 patent does not teach or suggest a rigid solid support comprising any type of molecular complex or co-stimulatory molecule.

WO 97/35991 has the same specification as the '884 patent. The teachings of WO 97/28191 and Latouche are discussed above.

c. WO 97/35991 in view of WO 97/28191 and Latouche

The teachings of WO 97/35991, WO 97/28191, and Latouche are discussed above.

[2] For example, the molecular complexes are single chain complexes (page 3, lines 7-25) and do not contain a immunoglobulin heavy chain variable region (*e.g.*, Figure 1C).

2. Differences between the prior art and the pending claims

The second factual inquiry under *Graham* is to ascertain the differences between the prior art and the claims at issue. 383 U.S. at 17. Each of the rejected claims recites a rigid solid support comprising (a) one or both of two particular molecular complexes and (b) at least one particular type of T cell affecting molecule. Nothing in any of the cited prior art teaches or suggests this combination. The combination of a co-stimulatory molecule and a molecular complex which can present an antigen is taught only in association with naturally occurring cells (fibroblasts in Latouche; antigen presenting cells in WO 97/28191). The combination of a rigid solid support and a molecular complex which can present an antigen, taught in the '411 patent, the '884 patent and WO 97/35991, does not include a co-stimulatory molecule.

3. Level of skill in the art

The third factual inquiry under *Graham v. John Deere Co.* is to resolve the level of skill in the pertinent art. 383 U.S. at 17. The person of ordinary skill is described in *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*:

> The person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art. The actual inventor's skill is not determinative. Factors that may be considered in determining level of skill include: type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field. Not all such factors may be present in every case, and one or more of them may predominate.

807 F.2d 955,962-63, 1 U.S.P.Q.2d 1196, 1201 (Fed. Cir. 1986).

The person of ordinary skill, being aware of all pertinent prior art relating to artificial antigen presenting cells, would have been aware of Albani, US 2002/0122818, which was cited in the Office Action and discussed above in connection with the rejections under 35 U.S.C.

§ 102(e). Albani teaches artificial antigen presenting cells (AAPCs), which are liposomes to which are anchored "an MHC:antigen complex" and, optionally, a co-stimulatory molecule. ¶¶ [0045]-[0046]. Albani teaches that the "free floating format" of the liposome is important for proper functioning of the AAPCs:

> [0050] The current invention's use of co-stimulatory, adhesion and other accessory molecules in a "free floating" format also helps to both anchor and direct the interaction between MHC:antigen:accessory molecule and T cell receptors by providing a means by which T cells in the sample will be presented with a structure more similar to that found in the natural state. Specifically, the MHC:antigen:accessory molecule complexes in conjunction with other functional molecules are able to migrate in proper orientation in the lipid bilayer of the liposome because of the use of a unique combination of lipids and surfactant molecules, namely an optimal ratio of phosphotidylcholine and cholesterol respectively, included in the liposome matrix. These provide particular protein presentation characteristics and easy protein migration properties to the surface of the liposome structure so that the MHC:antigen complexes can easily migrate to T cell binding loci similar to "capping" events seen in natural APCs. Moreover, as shown in the figures, the structure of our artificial APC liposomes allows for specific "capping" of the liposomes on the surface of the T cells to which the liposomes are bound.

Albani teaches that a liposome-based AAPC can be anchored to a solid support, but that only the lipid component itself – not any of the functional molecules it contains – is bound to the solid support. ¶ [0084].

The person of ordinary skill would also have understood that the "the definitive event governing a mature immune response when T lymphocyte or natural killer (NK) cells interact with target cells is the formation of an immunological synapse."[3] The immunological synapse is a "clearly organized pattern of protein complexes, several microns in diameter, that forms at the

[3] Qi *et al.*, *Proc. Natl. Acad. Sci. USA 98*, 6548-53, published on-line May 22, 2001, at page 6548, col. 1 ¶ 1 (internal references omitted); provided in the accompanying IDS.

junction between the membranes of the two cells" and requires that the proteins be able to move and reorganize in the cell membranes.[4]

4. Failure to establish a *prima facie* case of obviousness

The U.S. Patent and Trademark Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103; only when a *prima facie* case has been established does the burden shift to the applicants to provide evidence or argument in rebuttal. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1966 (Fed. Cir. 1993), *citing In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). In this case, the results of the factual inquiries carried out under *Graham* do not support a *prima facie* case that any of the rejected claims is obvious.

A *prima facie* case of obviousness requires that the cited references themselves or the knowledge generally available to one of ordinary skill in the art contain a suggestion or motivation to combine the reference teachings and that there must be a reasonable expectation of success that the combination would be successful. M.P.E.P. § 2142. Neither requirement is met.

As explained above, one of ordinary skill in the art would have known that formation of an immunological synapse between a T cell and an antigen presenting cell requires membrane fluidity. Albani, WO 97/28191, and Latouche all teach artificial antigen presenting cells which have fluid membranes. Being aware of these teachings, one of ordinary skill would not have been motivated to make a rigid solid support comprising a T cell affecting molecule and any of the molecular complexes taught in the '411 patent, the '884 patent, or WO 97/359911 because the ordinary artisan would not have had a reasonable expectation that the molecules would have been able to reorganize into the required immunological synapse. Yet, unexpectedly, rigid solid

[4] *Id.*

supports as claimed in this application both induce and expand antigen-specific cytotoxic T lymphocyte populations. See Examples 2 and 4.

The Office Action has not properly assessed the scope and content of the prior art, the differences between the prior art and the claimed methods, or the level of skill in the art and has not made a *prima facie* case of obviousness.

Applicants respectfully request withdrawal of the rejection.

Non-statutory Obviousness-Type Double Patenting Rejections

The Office Action makes two non-statutory obviousness-type double patenting rejections of claims 1-15, 23-29, 37, 39-41, 46-50, 60-62, 64, and 65 over the following combinations of references:

- claims 1-104 of U.S. Patent 6,268,411 in view of WO 97/35991, WO 97/28191, and Latouche (item 16 of the Office Action); and
- claims 1, 2, and 4-10 of U.S. Patent 6,015,884 in view of WO 97/35991, WO 97/28191, and Latouche (item 19 of the Office Action).

Applicants respectfully traverse the rejections.

An obviousness-type double patenting analysis parallels an analysis under 35 U.S.C. § 103(a) except that the disclosure of the cited patent is not considered prior art. *In re Braat,* 937 F.2d 589, 592, 19 U.S.P.Q.2d (BNA) 1289, 1291-92 (Fed. Cir. 1991); *In re Braithwaite*, 379 F.2d 594, 600, footnote 4, 154 U.S.P.Q. (BNA) 29, 34, footnote 4 (C.C.P.A. 1967). Thus, the arguments made above to rebut the rejection under 35 U.S.C. § 103(a) apply with equal force to the obviousness-type double patenting rejections and are incorporated herein.

Please withdraw the rejections.

Respectfully submitted,

BANNER & WITCOFF, LTD.

/Lisa M. Hemmendinger/

Date: March 23, 2007 By: _____

Lisa M. Hemmendinger

Customer Number: 22907 Registration No. 42,653